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(21) Application number: **01122739**(22) Date of filing: **18.05.88**(30) Priority: **18.05.88 JP 36311819**(71) Applicant: **MITSUBISHI KASEI CORP**

(72) Inventor: **ODA KOICHIRO**  
**INAMORI TAKESHI**

**(54) SLIGHTLY SOLUBLE DRUG COMPOSITION****(57) Abstract**

**PURPOSE:** To obtain a slightly soluble drug composition having extremely improved eluting effects, durable supersaturation phenomena, improved production efficiency and reduced production cost by rapidly removing a solvent from a solution or suspension having dissolved or suspended a slightly soluble drug and a carrier in an organic solvent.

**CONSTITUTION:** A solvent is abruptly removed from a solution or suspension having dissolved or suspended a

slightly soluble drug and a carrier (e.g., polyvinyl pyrrolidone) in an organic solvent (e.g., methylene chloride or methanol). When a drug such as indomethacin, griseofulvin or phenytoin having  $\leq 100 \mu\text{g/ml}$  solubility is used as the slightly soluble drug, excellently improving effects on solubility (dissolution rate and amount of dissolution) are shown. In this method, noncrystallization of slightly soluble drug is promoted by abrupt removal of the solvent.

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## Reference 4

Partial Translation

JP Patent Application (Unexameind) Disclosure No. 02-049720;

February 20, 1990

Title of the invention: Hardly soluble drug composition

JP Patent Application No. 01-122759; May 18, 1989

Priority: May 18, 1988; JP Patent Application No. 63-119191

Inventors: Oda Koichiro; Inamori Takeshi.

Applicant: Mitsubishi Kasei Corporation (Tokyo, Japan)

## Claims:

1. Hardly soluble drug composition obtainable by abruptly removing the solvent from a solution or a suspension wherein a hardly soluble drug and a carrier are dissolved with or suspended in an organic solvent.
2. Composition according to Claim 1, characterised in that the solubility of a hardly soluble drug to water is at most 100 µg/ml.
3. Composition according to Claim 1 or 2, characterised in that the carrier is a hydrophilic polymer compound and/or hydrophilic inorganic fine particles.
4. Composition according to Claim 3, characterised in that the hydrophilic polymer compound is at least one compound chosen from the group consisting of polyvinylpyrrolidone, crystalline cellulose, cross-linked

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carboxymethyl cellulose, polyethylene glycol, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose and partially alpha-starch.

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Detailed explanation of the invention:

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[page 3, lower left column, lines 6 to 14]

Example 1:

50 g Tritoqualine (manufactured by Mitsubishi Kasei Corporation) were dissolved in 1500 g methylene chloride, and further 50 g of polyvinyl pyrrolidone K-30 was dissolved. The solution was spray-dried using a Mobile Minor™ spray dryer (manufactured by Niro Atomizer) at disc-type atomiser rotation number 24000 rpm, at an exhaust gas temperature of 30 °C, at a sample feed rate of 40 g/minute to provide a hardly soluble drug composition (preparation 1).

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[page 3, lower right column, line 15 to page 4, upper left column, line 1]

Comparative Example:

The solvent was gradually removed from a suspension prepared by dissolving tritoqualine (10 g) in methylene chloride (130 g), and further suspending Aerosil 200® (10 g), using a vacuum dryer at 60°C, Δ70 cmHg over 2 hours to provide a composition which served as control. The present method belongs to conventional manufacturing processes.

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[page 4, upper left column, line 11 to lower left column, line 6]

Test Example 2:

Capsules were filled with preparation 1 prepared in said Example 1 and a control prepared in Comparative Example respectively; oral administration test of the preparations in the form of capsule to beagle dog was conducted whereby bioavailability was compared. The results are shown in Figure 2, wherein the present composition exhibited a far higher concentration in blood in comparison with the composition obtained by the conventional art, the results designated the improvement of bioavailability. Besides, average values at every measurement time of beagle dog used in the experiment are plotted in Figure 2.

The details of the experiment are shown below.

Trial subject (animal): female beagle dog (body weight 13 to 15 kg).

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Comparative cross-over trial about a group comprising 6 dogs.

Investigational drug: Preparation 1 and control are capsules containing 100 mg of tritoqualine, respectively.

Administration: After 24 hours fasting, a diet (200 g) was given. After 30 minutes, respective preparations together with water 30 ml were compulsorily orally administered, and fasting was effected for 6 hours after the administration while water-drinking was freely allowed.

Collecting blood specimen: A total of 10 points, comprising a point proximately before the administration and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 24 hours after the administration. 2 ml of blood a time were collected from vein of upper limb by using an injection cylinder containing heparin sodium. Serum was obtained by centrifugation at 15000 rpm for 1 minute.

Quantification: HPLC method using a fluorescent detector.

And the maximum drug concentration in blood and dispersion of area under curve (AUC) of [drug] concentration in blood 24 hours after the test, of respective beagle dogs, are shown in following table.

投与製剤	最高血中濃度 (ng/ml)	血中濃度下面積 0-24hr (ng·hr/ml)
対照剤	171.8 ± 29.8	768.7 ± 212.1
製剤 1	423.8 ± 35.8	1693.5 ± 217.8

[partial translation of the table]

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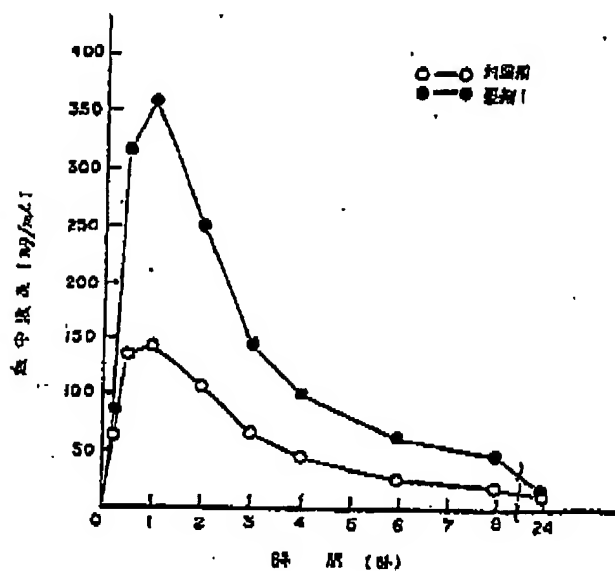
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Administered preparation	Maximum concentration in blood (ng/ml)	AUC of drug concentration in blood 0 to 24 hours (ng·hr/ml)
Control Preparation 1		

Figure 2

第 2 圖



Abscissa: time (hour); ordinate: concentration in blood (ng/ml);

○—○ control; ●—● preparation 1.